

APPLICANTS: Peled, *et al.*
SERIAL NUMBER: 10/774,843

REMARKS

Upon entry of this amendment, claims 401, 411, 412, 414, 416-419, 422-424, 437-438, 462, 464-467 and 469-481 will be pending in the application. Claims 401, 411, 412, 416, 419, 462, and 465 are amended herein. New claims 469-481 are added. Support for the amendments and new claims can be found throughout the as-filed specification. In support of the remarks and arguments stated *infra*, Applicants submit herewith a Declaration of Dr. Tony Peled under 37 C.F.R. § 1.132 (“Peled Declaration”). No new matter is added.

Claim Objections

Claim 416 is objected to for the recitation of the phrase “...any of claim 401”. *See*, Office Action at page 8. Claim 416 is amended herein to recite “The method of claim 401...”. Thus, this rejection is moot and should be withdrawn.

Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 419 and 465 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. *See*, Office Action at page 11. Claim 419 is amended to depend from claim 401 and claim 465 is amended to recite, “The transplantable cell preparation of claim 411...”. Thus, these rejections are moot and should be withdrawn.

Rejections Under 35 U.S.C. § 103(a)

Claims 401, 411, 412, 414, 416-419, 422-424, 437-438, 462, 464, and 466-467 are rejected under 35 U.S.C. § 103(a) as being unpatentable over US Patent Publication No. 2002/0159984 to Brown (“Brown”). Applicants traverse with respect to the claims, as amended.

Claims 401, 411, 412, and 462 (from which the remaining claims subject to the rejection depend) are amended herein to recite methods for *ex-vivo* expansion of hematopoietic stem cells by culturing the cells in the presence of 1.0 mM to 10 mM exogenously added nicotinamide, nicotinamide analog or nicotinamide derivative for a culture period resulting in expanding the hematopoietic stem cells and inhibiting differentiation of the CD34⁺ stem cells, as compared to CD34⁺ cells cultured in the presence of cytokines and nutrients without exogenously added nicotinamide.

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Brown does not teach or suggest using nicotinamide for expanding hematopoietic stem cells and inhibiting the differentiation of the CD34⁺stem cells; and most certainly, does not teach or suggest expanding hematopoietic stem cells and inhibiting the differentiation of the CD34⁺stem cells by using nicotinamide in the critical range of 1.0 mM to 10 mM, as required by the instant claims. At best, Brown merely lists nicotinamide, at a concentration of 4 mg/L, along with 44 other compounds, as a component of IMDM. *See*, for example, Brown at Table I, page 4, left column. Further, Brown mentions that nicotinamide is one of a number of "...various vitamins and co-factors, such as riboflavin, nicotinamide, folic acid, choline, biotin, and the like that may be required to sustain cell growth." *See*, for example, Brown at page 3, right hand column.

Although Brown does not explicitly teach or suggest using nicotinamide as required by instant claims, the Examiner asserts that "a culture medium supplemented with concentrations of about 4 mg/L (i.e., 0.033 mM) as taught by Brown could induce CD34+ cell expansion, absent evidence to the contrary". *See*, Office Action at page 6. In response to the Examiner's assertion, Applicants herein provided rebuttal evidence that the concentration of nicotinamide disclosed in Brown, *i.e.*, 4 mg/L, is insufficient for the expansion of hematopoietic stem cells and inhibition of CD34⁺ cell differentiation. As shown in the attached Peled Declaration, nicotinamide concentrations of up to 10 times the 4 mg/L nicotinamide disclosed by Brown are ineffective for *ex-vivo* expansion and inhibition of hematopoietic stem/progenitor cells, as compared with cells cultured in the presence of cytokines and nutrients alone (0.0 mM nicotinamide). *See*, Peled Declaration at pages 2-4 and at Figure 1. As such, Brown teaches away from claimed the invention by suggesting that nicotinamide is not useful for *ex-vivo* expansion and inhibition of differentiation of hematopoietic stem cells.

Additionally, based on the Examiner's assertion above that "a culture medium supplemented with concentrations of about 4 mg/L as taught by Brown could induce CD34+ cell expansion, absent evidence to the contrary", the Examiner further asserts that Brown "clearly identifies the criticality of discovering the optimum or workable ranges by routine experimentation". *See*, Office Action at page 6. As described in the Peled Declaration, it is clear that one of ordinary skill in the art, attempting to expand hematopoietic stem/progenitor cells, while inhibiting stem cell differentiation, using the culture medium taught in Brown, would conclude that nicotinamide is not useful for *ex-vivo* expansion and inhibition of differentiation of hematopoietic stem cells, as compared to cells cultured without exogenously added

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nicotinamide. As such, in view of the provided rebuttal evidence and contrary to the Examiner's contention, one skilled in the art would not optimize the concentration of nicotinamide taught by Brown to reach the critical amount of 1.0 mM to 10 mM exogenously added nicotinamide, required by the instant invention, by routine experimentation with predictable results.

Moreover, the data presented in the Peled Declaration and the working example provided in the instant specification at Example 5 readily demonstrates that the present invention provides unexpected and superior properties not taught or suggested by the prior art, *e.g.*, that the critical range 1.0 mM to 10 mM exogenously added nicotinamide, nicotinamide analog or nicotinamide derivative provides extensive expansion of the population of hematopoietic stem cells while inhibiting differentiation of the CD34+ stem cells *ex vivo*.

For the foregoing reasons, Applicants submit that claims 401, 411, 412, and 462 (from which the remaining claims subject to the rejection depend) are not obvious in view of Brown.

Moreover, new claims 469-474, which depend from the above-mentioned independent claims, are also not obvious in view of Brown. New claim 475 requires culturing the cells in the presence of an effective amount of exogenously added nicotinamide, nicotinamide analog or nicotinamide derivative for a culture period sufficient to expand the population of hematopoietic stem cells while inhibiting differentiation of the CD34+ stem cells *ex-vivo*. As described in detail *supra*, Brown does not teach or suggest using any effective amounts of nicotinamide sufficient for expanding hematopoietic stem cells and inhibiting the differentiation of the CD34⁺ stem cells which isn't taught or suggested by Brown. As such, new claim 475 is also not obvious in view of Brown.

Applicants respectfully request reconsideration and withdrawal of the present rejection.

Claims 401, 437, and 438 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Brown in view of Banasik et al., 1992 JBC, 1569-1575 ("Banasik"). *See*, Office Action at page 12. Applicants traverse with respect to the claims, as amended.

As described above, Brown does not teach or suggest using nicotinamide for expanding hematopoietic stem cells and inhibiting the differentiation of the CD34⁺ stem cells and does not teach or suggest using the critical range of 1.0 mM to 10 mM exogenously added nicotinamide, nicotinamide analog or nicotinamide derivative, as required by the instant claims.

Banasik does not cure the deficiencies of Brown. By contrast, Banasik merely discloses that benzamide, as well as nicotinamide, is an inhibitor of poly(ADP-ribose) synthetase activity.

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Banasik is silent with regard to the use of nicotinamide or nicotinamide analogs for expansion and inhibition of differentiation of hematopoietic stem cells.

As such, Applicants submit that the present invention is not obvious in view of the combination of Brown and Banasik. Applicants respectfully request reconsideration and withdrawal of the present rejection.

Rejections Under 35 U.S.C. § 102(b)

Claim 411 is rejected under 35 U.S.C. § 102(b) as anticipated by U.S. Patent No. 5,945,337 to Brown (the “‘337 patent”). *See*, Office Action at page 7. Claims 401, 412, 414, 416-419, 422-424, 464, and 466 are also rejected under 35 U.S.C. § 102(b) as being anticipated by the ‘337 patent. *See*, Office Action at page 9. Applicants traverse with respect to the claims, as amended.

Claims 401, 411, and 412 (from which the remaining claims subject to the rejection depend) recite culturing the cells in the presence of 1.0 mM to 10 mM exogenously added nicotinamide, nicotinamide analog or nicotinamide derivative, which is not taught by the ‘337 patent.

As such, Applicants submit that claims 401, 411, and 412 (from which the remaining claims subject to the rejection depend) are not anticipated by the ‘337 patent. Moreover, new claims 469-474, which depend from the above-mentioned independent claims, are also not anticipated by the ‘337 patent.

New claim 475 requires culturing the cells in the presence of an effective amount of exogenously added nicotinamide, nicotinamide analog or nicotinamide derivative for a culture period sufficient to expand the population of hematopoietic stem cells while inhibiting differentiation of the CD34+ stem cells *ex-vivo*, which is not taught by the ‘337 patent. As such, new claim 475 is also not anticipated by the ‘337 patent.

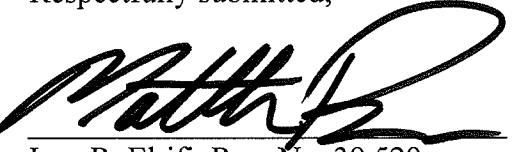
Reconsideration and withdrawal of the present rejection are respectfully requested.

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On the basis of the foregoing amendments, Applicants respectfully submit that the pending claims are in condition for allowance. Should any questions or issues arise concerning this application, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,



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